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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,530	03/06/2002	William Alexander Denny	PC17523A	5543

28940 7590 02/14/2006

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 02/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,530	DENNY ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2005, 24 June 2004& 08 October*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *3,6,7,10 and 12-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5 and 11* is/are rejected.

7)☒ Claim(s) *8 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/6/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to a petition decision made on 4/29/05 and a response to a restriction received on 10/8/03. Applicants' amendments to the claims filed on 6/24/04 are currently being considered. There are twenty-two claims pending and seven under consideration. Claims 1, 2, 4, 5, 8, and 9 are compound claims. Claim 11 is a composition claim. This is the first action on the merits. The application concerns some 2-amino-pteridin-7-one compounds, compositions, and uses thereof.

2. The Examiner also wishes to apologize for yet another delay in the prosecution of this case. However, the case was not placed on his docket after the petition decision was made in April of last year.

Election/Restrictions

3. Applicant's election with traverse of Group I in the reply filed on 10/8/03 is acknowledged. The traversal is on the ground(s) that compound **1** of Ott (Chem. Ber.) does not fit the limitations of claim 1 and that the Examiner may not reject claims in a restriction. This is not found persuasive because compound **4** of Ott (Chem. Ber.) certainly fits the limitations of claim 1 with R^2 = benzyl, W = S, R^4 = amino, R^6 = carboethoxy, and R^8 = H. No claims have been rejected and section 13.2 of the PCT rules clearly require that any, ""special technical features" shall mean those technical features that define a contribution which each of the claimed

inventions, considered as a whole, makes over the prior art." Since the formula of claim 1 does not represent an advance over the prior art it cannot be a "special technical feature". Thus, the application lacks the requirement of unity of invention. The requirement is still deemed proper and is therefore made FINAL.

4. Applicants were requested to elect a single use, which they wished examined. Applicants did not select a use. Thus, no therapeutic use claims will be examined.

5. Claims 3, 6, 7, 10, and 12-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/8/03.

6. Objection is made to claims 1, 8, 9, and 11 as containing non-elected subject matter. The claims are drawn to multiple inventions for reasons set forth in the above requirement for restriction. The claimed compounds, compositions, and methods that employ them present a variable core. The formulas of claims 1, 2, and 4 contain compounds drawn to the non-elected inventions. The compounds listed in claims 8 and 9 contain compounds other than those of the elected 2-aminopteridin-7-ones. Deletion of W = S, SO, or SO_2 from the formula of claim 1,

deletion of R^6 = hydroxy from the formulas of claims 1, 2, and 4, and deletion of the non-elected species from claims 8 and 9 will overcome the rejection.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The proviso in the last two lines of claim 1 lacks description. Nowhere in the specification is such a relationship linking the description between radicals R^6 and R^8 described or between radicals R^8 and Z. Such negative limitations require description. In *Ex parte Grasselli, et al.* 231 USPQ 393, decided June 30, 1983, the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences said: "we agree with the examiner's position of record that the negative limitations recited in the present claims, which did not appear in the specification as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112." "It might be added that the express exclusion of certain elements implies the permissible inclusion of all other elements not so

expressly excluded. This clearly illustrates that such negative limitations do, in fact, introduce new concepts."

8. Claims 1, 2, 4, 5, and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making the salts, the esters listed in lines 2-4, page 16 and the amides listed in lines 9-11, page 16 of the specification, does not reasonably provide enablement for making any prodrug, esters generally, or amides generally. The specification does not enable one skilled in the art of medicinal chemistry to use or make the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to

predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

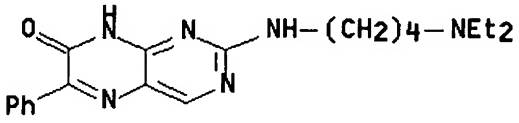
b) The direction concerning the prodrugs is found in lines 11-18, page 15 and lines 16-22, page 16 of the specification. c) There is no working example of a prodrug of a compound the formula given in claim 1. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) in the first sentence, third

paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim 1 as well as the presently unknown list of potential prodrug derivatives embraced by claim 1.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

Allowable Subject Matter

9. Claims 8 and 9 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The following is a statement of reasons for the indication of allowable subject matter: Applicants compounds are patentable over Bondinell (WO 2002076985 A1). The compound shown below is found in the reference and fits the formula of claim 1 with W = NH, R^2 = butyl substituted by diethylamino, $R^4 = R^8$ = hydrogen, and R^6 = phenyl. However, Bondinell (WO 2002076985 A1) is an incompetent reference because of Applicants effective filing date of 6/21/00.



Conclusion

10. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system,

contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

11. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571) 273-8300. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 9:00am to 5:30pm, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, SPE of Art Unit 1624, at (571)-272-0661.

Thomas C. McKenzie, Ph.D.
Primary Examiner
Art Unit 1624

TCMcK/me